



QUANTITATIVE & SYSTEMS BIOLOGY COLLOQUIUM: A Systems Biology approach to understand drug mechanism of action

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About The Speaker:

Professor Le Roch has over 25 years of expertise in drug discovery and functional genomics in eukaryotic organisms, with a particular focus on apicomplexan parasites, including *Plasmodium falciparum*, the protozoan responsible for the deadliest form of malaria in humans. She received her BA. in biochemistry/chemistry in 1995 from the University of Paris - Sorbonne, France. She then joined the laboratory of Prof. M. Doenhoff in North Wales University, UK as an Assistant Researcher to work on the development of a vaccine against Schistosomiasis, also known as bilharzia, a parasitic disease that affect 200 million people worldwide. Following this research experience, Dr. Le Roch obtained her master's degree in Parasitology in 1997 at the University of Lille II, France and the University of Oxford, UK where she worked on the characterization of molecular components of *Pneumocystis carinii*, an opportunistic pathogen that occurs in immunosuppressed populations. She completed her Ph.D. in June 2001 at the University of Paris - Sorbonne under the supervision of Prof C. Deorig. Her work explored the role of protein kinases and signal transduction in the control of the *P. falciparum*'s life cycle. In 2001, as a postdoctoral fellow, Dr. Le Roch joined the Scripps Research Institute, USA, where she worked with Prof. E. Winzeler on the functional genomics of malaria parasites. In January 2004, as a research fellow, she joined the Genomic Institute of the Novartis Research Foundation (GNF) where she laid the foundation for Novartis's malaria drug discovery program. Since April 2006, as an Assistant, Associate and now Professor and Director of the Center for Infectious Disease and Vector Research at the University of California Riverside, Dr. Le Roch broadened her research to include functional genomics and systems biology approaches to investigate host-pathogen interactions and identify key molecular pathways underlying parasite development, with a particular focus on gene regulation, epigenetics, chromatin structure, non-coding RNAs and RNA binding proteins. Recently, she developed a powerful systems biology pipeline to identify complex drug mechanisms of action of natural products against *Plasmodium*. As a Principal Investigator on multiple well-funded projects, Dr. Le Roch has successfully managed, collaborated on, and published numerous high-impact peer-reviewed articles. Her expertise in genomics and molecular biology techniques, as well as her extensive experience in acquiring, handling, and analyzing large datasets, is reflected in over 135 peer-reviewed publications, 14 book chapters, and three US patents.

For more information see GoogleScholar: Citations: 25261; h-index:56; i10-index:122
<https://scholar.google.com/citations?user=wcZCugQAAAAJ&hl=en&oi=ao>

Abstract:

Despite decades of control efforts, malaria continues to impose a substantial burden on vulnerable populations, in part because *Plasmodium falciparum* repeatedly evolves resistance to new drugs and other interventions. There remains an urgent need for antimalarial compounds with novel mechanisms of action that are effective against drug-resistant parasites and active across multiple stages of the parasite life cycle. Our lab has developed a chemical and systems biology pipeline to characterize MED6-189, a synthetic analog of the kalihinol family of isocyanoterpene natural products. MED6-189 displays potent activity against both drug-sensitive and drug-resistant *P. falciparum* strains and inhibits asexual blood-stage replication as well as sexual differentiation. In a humanized mouse model of malaria, MED6-189 demonstrated strong antimalarial efficacy with no apparent hemolytic activity or overt toxicity. Combining transcriptomic and metabolomic profiling as well as chemical pull-down and thermal-shift experiments, we found that MED6-189 primarily disrupts functions associated with the parasite apicoplast, an essential organelle involved in parasite development and host-cell invasion. Although a specific molecular target has not yet been identified, our findings indicate that MED6-189 interferes with lipid biogenesis and intracellular trafficking. Resistance selection and genomic analysis further identified a mutation in *PfSec13*, which encodes a component of the parasite secretory machinery, that reduces susceptibility to the compound. Together, these results reveal a distinctive mechanism of antimalarial activity and demonstrate that MED6-189 combines high potency, activity against resistant parasites, and a favorable in vivo therapeutic profile, supporting its further development as a promising addition to the antimalarial drug pipeline.

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10:30 AM – 11:45 AM

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